

application issues as a patent and the obviousness-type double patenting rejection remains in the present case, an appropriate terminal disclaimer will be filed.

Claims 1-6, 9, 11-13, 15, and 17-25 stand rejected under 35 U.S.C. § 112, first paragraph. The Office believes that the specification is enabling for a method of reducing zvegf3 activity in a mammal, but does not provide enablement for the full scope of the claims.

Applicant respectfully traverses this ground of rejection. Because the Office has analyzed the claims in terms of the individual *Wands* factors, each of these factors will be addressed individually. However, Applicant wishes to note that it is improper to conclude that a disclosure is not enabling based on an analysis of only one of these factors while ignoring one or more of the others. Any conclusion of non-enablement must be based on the evidence as a whole. MPEP 2164.01(a).

The Nature of the Invention

Applicant agrees that the present claims are drawn to methods of reducing cell proliferation or extracellular matrix production in a mammal, methods of treating fibrosis in a mammal, and methods of reducing stellate cell activation in a mammal. The claims encompass, in general, antibody treatment for mammalian disorders. The Office has again rejected the claims as a group, and has not addressed the patentability of individual claims or groups of claims. Applicant submits that the claims do not stand or fall together.

Although the Office has correctly characterized the claims as being drawn to “methods of reducing cell proliferation or extracellular matrix production in a mammal” and “methods of reducing stellate cell activation in a mammal” (Office Action at page 4), subsequent discussion of the claims appears to be based on an alternative characterization. More specifically, the Office states at page 8 that “it is unlikely that [] administration of zvegf3 antibody alone would be able to halt cell proliferation, extracellular matrix and stellate cell activation associated with fibrosis” and that “it is unlikely that any single agent will effectively stop renal fibrosis” (emphasis added). The claims do not require halting or effectively stopping any disease or related process; they recite “reducing cell proliferation or extracellular matrix production” (claim 1), “treating fibrosis” (claim 11), and “reducing stellate cell activation” (claim 17). The terms “treat” and “treatment” are defined at page 4 of the specification “to denote therapeutic and prophylactic interventions that favorably alter a pathological state” and to include “procedures that moderate or reverse the progression of, reduce the severity of, prevent, or cure a disease.” The claims do not require a complete inhibition or halting of stellate cell activation or any other process.

The Breadth of the Claims

The Office states at page 5 of the Office Action, "The claims are very broad." Applicant disagrees with this blanket characterization; claims of varying scope have been presented. Claim 1 is directed to a method of reducing cell proliferation or extracellular matrix production in a mammal using a zvegf3 antagonist antibody that specifically binds to a defined dimeric protein. Claim 2 is directed to a method of reducing proliferation of certain cell types. Claim 3 recites that extracellular matrix production is reduced. Claims 4-6 recite fibroproliferative disorders of specific tissues. Claims 9, 22, and 23 further define the antibody. Claim 11 is directed to a method of treating fibrosis using the antibody recited in claim 1. Claims 12 and 13 recite that the fibrosis is liver fibrosis or kidney fibrosis, respectively. Claims 15, 24, and 25 further define the antibody. Claim 17 is directed to a method of reducing stellate cell activation in a mammal using the antibody recited in claims 1 and 11. Claim 18 recites that the stellate cells are liver stellate cells. Claims 19-21 further define the antibody.

The Office has failed to differentiate among the 20 pending claims and their varying scopes, and has instead applied the same broad-brush rejection to all claims, apparently disregarding recited limitations. As stated above, Applicant submits that the claims do not stand or fall together.

Claim 2 is directed to a method of reducing cell proliferation wherein proliferation of mesangial, endothelial, smooth muscle, fibroblast, osteoblast, osteoclast, stellate, or interstitial cells is reduced. Each of these cell types is known to express PDGF receptors and to be responsive to PDGFs. Because zvegf3 is mitogenic (e.g., specification at pages 36-37, 38-39, and 40-41) and exerts its activity by binding to and activating PDGF receptors (specification at page 4, lines 19-23), one skilled in the art would reasonably conclude that a zvegf3 antagonist as recited in claim 2 could be used to reduce proliferation of these cell types.

With regard to the specific cell types recited in claim 2, Applicant wishes to direct the Office to the following evidence. Osteoblasts respond to zvegf3 as disclosed in Applicants' specification at pages 38-39. See also, Fujii et al., *Histochem. Cell Biol.* 112:131-138, 1999 at page 133 (Table 1), which discloses expression of PDGF α receptor mRNA in osteoblasts during several phases of fracture healing. Stellate cells bind and respond to zvegf3 as shown in Applicant's specification at pages 36-37 and produce TGF- β in response to stimulation by zvegf3 (page 40). Mitogenic activity of zvegf3 on mesangial cells is disclosed in Applicant's specification at pages 40-41. Mesangial, endothelial, smooth muscle, fibroblast, osteoclast, and interstitial cells are also known in the art to express cell-surface PDGF receptors. See, for example, Marx et

al., *J. Clin. Invest.* 93:131-139, 1994 at page 131, left column, and page 133, right column (endothelial cells), Hart et al., *J. Biol. Chem.* 262:10780-10785, 1987 at page 10780 left column (fibroblasts and smooth muscle cells); Fujii et al. (*ibid.*) at page 133 (osteoclasts); Tang et al., *Am. J. Pathol.* 148:1169-1180, 1996 at page 1178, left column (interstitial cells); Heldin and Westermark, *Physiological Reviews* 79:1283-1316, 1999 at page 1288 (fibroblasts, mesangial cells, endothelial cells, smooth muscle cells). Copies of the Marx, Hart, Fujii, Tang, and Heldin references are enclosed.

Claim 3 recites a method wherein extracellular matrix production is reduced. As disclosed by Friedman (*Seminars in Liver Disease* 19:129-140, 1999; of record) at page 129, hepatic fibrosis is characterized by an overall increase in extracellular matrix. TGF- β 1 is the “most dominant fibrogenic cytokine in hepatic fibrosis” (Friedman at 135), and a major source of this cytokine is autocrine expression (*id.*). As discussed above, Applicant has demonstrated that zvegf3 promotes stellate cell mitogenesis and TGF- β production, thus zvegf3 would also be expected to promote extracellular matrix production. One skilled in the art would therefore reasonably conclude that an antibody to zvegf3 could be used to reduce extracellular matrix production.

Claim 4 recites that the mammal is suffereing from a fibroproliferative disorder of the liver, and claim 12 recites liver fibrosis. As disclosed in Applicant's specification at pages 39-40, administration of zvegf3 (via an adenovirus vector) to experimental animals resulted in proliferation of stellate cells and/or fibroblasts in the liver. Stellate cells “are a major cellular source of extracellular matrix production during liver injury.” Friedman (*ibid.*) at page 132, left column. Applicant has also disclosed that zvegf3 is mitogenic for stellate cells (specification at pages 36-37) and stimulates TGF- β production by stellate cells (specification at page 40), both of which activities are known in the art to be relevant to hepatic fibrosis.

Claim 5 recites that the mammal is suffereing from a fibroproliferative disorder of the kidney, and claim 13 recites kidney fibrosis. Friedman (*ibid.*) discloses at pages 132, right column, that mesangial cells play a role in renal injury that parallels that of stellate cells in hepatic injury. Applicant has disclosed experimental results showing that zvegf3 is mitogenic for mesangial cells (specification at pages 40-41). In addition, administration of a zvegf3-encoding adenoviral vector to experimental animals produced changes in the kidneys that were consistent with fibrosis (specification at pages 39-40).

Claim 6 recites that the mammal is suffering from a fibroproliferative disorder of bone. Applicant has demonstrated a mitogenic effect of zvegf3 on osteoblasts. A defect in osteoblast differentiation and function is thought to be a major cause in osteopetrosis (specification at page 12).

Claims 17-21 recite a method of reducing stellate cell activation. Zvegf3 is mitogenic for stellate cells (specification at pages 36-37) and stimulates TGF- β production by stellate cells (specification at page 40). Friedman (*ibid.*) discloses at pages 132-135 that cytokines, including PDGF, are stimulators of stellate cell activation; that cell proliferation is a characteristic of activated stellate cells; and that TGF- β 1 is upregulated in activated stellate cells. Applicant further discloses at pages 39-40 that administration of zvegf3 (via an adenovirus vector) to experimental animals resulted in proliferation of stellate cells and/or fibroblasts in the liver.

In summary, Applicant submits that the disclosure is commensurate with the breadth of the claims, and that support for each claim is found within the specification as filed.

The Unpredictability of the Art and the State of the Prior Art

As discussed above, Applicant believes that the Office has mischaracterized the pending claims as being directed to “effectively stop[ping] renal fibrosis” and “halt[ing] cell proliferation, extracellular matrix and stellate cell activation associated with fibrosis” in its discussion at page 8 of the Office Action. The Office has also stated at page 8 that “it is unlikely that [] administration of zvegf3 antibody alone would be able to halt cell proliferation, extracellular matrix and stellate cell activation associated with fibrosis.”

Applicant respectfully submits that the rejection cannot be sustained in view of a correct reading of the claims. Applicant’s claims are drawn to methods of “reducing” or “treating” certain processes as discussed above. Furthermore, the specification teaches the use of zvegf3 antibodies in combination with inhibitors of other mitogenic factors, and the claims recite “comprising administering to the mammal a composition comprising a zvegf3 antagonist”. Hence, the claims include combination therapies. None of the claims requires that the zvegf3 antagonist alone provide complete cessation or reversal of any process or condition.

Applicant’s specification discloses data showing the effects of zvegf3 on cellular process, including cell proliferation, that are relevant to extracellular matrix production, stellate cell activation, and fibrosis in a mammal. These data include both *in vitro* results and *in vivo* results. In view of these experimental data, it is believed that the claims, when properly construed, are fully supported by the specification.

The Office has cited Kitamura, Dhanesekaran, Mann, and Yu for the proposition that “the relevant art recognizes that cell proliferative diseases such as cancer can be due to dominant genetic mutations which can function independent of other factors.” However, the Office has provided no evidence that zvegf3 does not promote

cell proliferation, extracellular matrix production, fibrosis, or stellate cell activation. Moreover, the claims recite methods of reducing or treating these processes, and thus do not recite uses of zvegf3 that do not achieve the recited result. Even assuming, *arguendo*, that the cited references support the Office's contention of inoperability for certain embodiments of the claimed invention, the presence of inoperative embodiments does not necessarily render a claim nonenabled. MPEP 2164.08(b).

Yu was cited in support of the proposition that "it is unlikely that any single agent will effectively stop renal fibrosis." Applicant's claims 11-15 and 24-25 are directed to a method of treating fibrosis, wherein "treating" includes "favorably alter[ing] a pathological state" and "reduc[ing] the severity of . . . a disease." The art recognizes that antagonists of the PDGF receptor pathway are useful in reducing fibroproliferative responses, including fibroproliferative responses in the kidney. See, for example, Johnson et al., *J. Exp. Med.* 175:1413-1416, 1992 and Yagi et al., *Gen. Pharmac.* 31:765-773, 1998, which were previously cited by Applicant. Thus, notwithstanding the disclosure of Yu, the art clearly recognizes that antagonists of a single growth factor are useful in reducing fibroproliferative processes.

Working Examples and Guidance in the Specification

The Office has repeated its allegation that "The specification has no working examples, whatsoever, demonstrating administration of a zvegf3 antibody to a mammal."

Applicant respectfully submits that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph does not turn on whether an example is disclosed. See, MPEP 2164.02. The absence of working examples will not by itself render the invention non-enabled. *Id.*

Claims 1-6, 9, 22, and 23 are directed to a method of reducing cell proliferation or extracellular matrix production. Applicant has disclosed experimental results demonstrating that zvegf3 growth factor domain protein is mitogenic for cells expressing cell-surface PDGF α -receptor subunit (specification at page 4) and, in particular, for mesangial cells (pp. 40-41), stellate cells (pp. 36-37), and osteoblasts (p. 38). In view of Applicant's disclosure and the art discussed above, one of ordinary skill in the art would expect the zvegf3 growth factor domain to be mitogenic for other cells that express the PDGF α -receptor subunit, such as endothelial cells, smooth muscle cells, fibroblasts, osteoclasts, and interstitial cells. Hence, one of ordinary skill in the art would reasonably conclude that if zvegf3 is mitogenic for these cells, then an antibody that inhibits zvegf3 biological activity would be useful in reducing proliferation of these cells. Applicant has further shown, in Example 13, that the zvegf3 growth factor domain

protein stimulates TGF- β 1 production by hepatic stellate cells. TGF- β 1 is known to be profibrogenic (Li et al. (previously cited) at page 620, right column) and is upregulated in activated stellate cells (Friedman, *ibid.*, page 135, left column). Activated stellate cells are the primary source of extracellular matrix in hepatic fibrosis (Friedman at page 129, left column), and TGF- β 1 is important in extracellular matrix remodelling (Friedman at page 135). Based on Applicant's disclosure, one of ordinary skill in the art would reasonably conclude that an antibody that inhibits zvegf3 biological activity would be useful in reducing extracellular matrix production.

Claims 11, 12, 13, 15, and 23-25 are directed to a method of treating fibrosis in a mammal using a zvegf3 antagonist antibody that specifically binds to a defined dimeric protein. Claim 12 recites that the fibrosis is liver fibrosis, and claim 13 recites that the fibrosis is kidney fibrosis. Applicant has shown a correlation between zvegf3 overexpression and both liver fibrosis and kidney fibrosis in an animal model (specification at pages 39-40). There is thus a reasonable correlation between Applicant's disclosure and claims 11, 12, 13, 15, and 23-25.

Claims 17-21 are directed to a method of reducing stellate cell activation in a mammal. As discussed above, Applicant has disclosed experimental results showing that zvegf3 proteins promote stellate cell proliferation and upregulation of TGF- β production by stellate cells. Proliferation and TGF- β upregulation are markers of stellate cell activation (e.g., Li et al. at page 620, left column and page 622, left column). On the basis of the disclosed results, one of ordinary skill in the art would reasonably conclude that the recited antibodies could be used to reduce stellate cell activation in a mammal.

Quantity of Experimentation

The Office contends that "the art teaches that there are cellular mechanism[s] independent of zvegf3 activity (such as constitutively active mutants) which result in activation of cell proliferation, extracellular matrix production and stellate cell activation" and that "one of skill in the art could not reasonably predict that the zvegf3 antibody could be used to treat any cell proliferative disorder without specific supporting evidence." The Office considers the amount of additional experimentation required to be undue.

One of ordinary skill in the art can readily determine whether or not a specific cell responds to zvegf3 using conventional assays, such as those disclosed at pages 19, 36-37, 38, and 40-41 of Applicant's specification. As would be evident to one skilled in the art, antibodies can be used in conjunction with these assays to determine the ability of the antibodies to reduce the effects of zvegf3 on the target cells. Activities of zvegf3 and anti-zvegf3 antibodies can be further analyzed using animal models as

disclosed at pages 19-20, 33, and 39-40 of Applicant's specification. These and other assays are known in the art and are within the scope of routine experimentation in the art.

Level of Skill in the Art

Applicant agrees that the level of skill in the art is high. Those skilled in the art routinely carry out complex, difficult experiments.

In view of the scope of the claims, the state of the art and level of skill in the art, and the content of Applicant's disclosure, it is believed that the pending claims are fully enabled. What experimentation would be required is of a nature that would be regarded as routine in the art. Reconsideration and withdrawal of the rejection under § 112, first paragraph, are requested.

Applicants believe that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6673.

Respectfully Submitted,



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Enclosures:

Amendment Fee Transmittal (in duplicate)
5 References
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